METHOD FOR SEPARATING AN ANALYTE FROM A SAMPLE

PARENT APPLICATION DATA

[0001] This application is a division of co-pending U.S. application Ser. No. 09/331,911 filed Jun. 25, 1999 as a national stage entry (371) of International Application PCT/US98/27632 filed Dec. 24, 1998 which international application claims priority from U.S. application Ser. No. 09/115,454 filed Jul. 14, 1998, now abandoned. All of these applications are incorporated by reference herein for all purposes.

FIELD OF THE INVENTION

[0002] This invention relates to a method for separating an analyte from a sample.

BACKGROUND OF THE INVENTION

[0003] The analysis of clinical or environmental fluids generally involves a series of chemical, optical, electrical, mechanical, or thermal processing steps on the fluid samples. Whether incorporated into a bench-top instrument, a disposable cartridge, or a combination of the two, such processing involves complex fluidic assemblies and processing algorithms.

[0004] Contemporary biomedical processing instruments are typically complex, robotically operated devices that move boluses of liquids automatically from one processing region to another. Prior cartridges have also generally processed a fluid sample as a fluid plug or bolus, moving a small quantity of sample from one region to another, where a further process is conducted. For example, Anderson et al. disclose such a device for sample processing in an article entitled "*Microfluidic Biochemical Analysis System*", Transducers '97, 1997 International Conference on Solid-State Sensors and Actuators, Chicago, Jun. 16-19, 1997, pg. 477-480.

[0005] In many analytical procedures, relatively large volumes of liquid (from microliters to milliliters) must be analyzed. Using the bolus approach, such volumes must be held in a container while each operation is performed. While the bolus approach allows for the implementation of complex processing methods, the volume of the fluid sample which can be processed is limited by the size of the individual processing regions, especially where the sample is transiently processed. Thus, the lowest detectable concentration of analyte, i.e. sensitivity, in any assay based on a bolus approach is also limited.

[0006] If the container is fabricated with integrated circuit chip technologies (microfluidic chips), the microfabricated chip must be very large to accommodate the relatively large volumes needed to detect a low concentration of analyte. For example, for a 100 microliter volume, a chip at least 1 cm on a side would be required for each bolus processing region. Such a large chip would not only be expensive, but would also defeat the purpose of miniaturization, especially for many types of disposable medical or environmental diagnostic uses.

[0007] Present day microfluidic technology has focused on picoliter, nanoliter, and microliter fluid volumes. These small volumes are not practical for many realistic diagnostic applications. As shown in FIG. **1**, the full range of chemical concentrations which one may want to detect in biological samples spans at least 20 orders of magnitude (from 6 copies/mL to 6×10^{20} copies/mL). Therefore, a cartridge for detecting the full range of potential analytes (especially DNA which exists in very low concentration in most biological samples) should be capable of processing large as well as small sample volumes.

[0008] Of special interest is the detection of low copy concentrations of analytes such as DNA, in which case large sample volumes are required. For example, the minimum theoretically detectable concentration for DNA probe assays necessitates large sample sizes, such as about 10^{-4} liters or more. In detecting infectious diseases, gram negative bacteria can be present at less than 10 copies per milliliter of blood, cryptosporidium generally appears as only a few copies per gallon of drinking water, concentrated biothreat agents, e.g. anthrax, at less than 100 copies per milliliter of water, and food poisoning agents, such as *E. coli* and *salmonella*, may be manifested in less than 10 copies per gram of food.

[0009] Thus, sample volumes needed to detect such infectious disease analytes would be larger than those required for detecting analytes present in higher concentrations, as in most clinical and immunochemistry assays. In addition, in the case of more concentrated analytes, such as those in immunoassays and clinical chemistry assays, a large volume sample provides more options for choosing less sensitive detection means, as well as the ability to divide the sample and detect multiple analytes. On the other hand, despite the merits of large sample volumes, it is generally recognized that unique functions can be realized with microfluidic structures, which are generally not compatible with large volumes.

SUMMARY

[0010] The processing devices and methodology of the present invention elegantly resolve the dilemma between large sample volumes and microfluidic structures by incorporating microfluidic chips or components into larger cartridges having any desired combination of microscale to macroscale channels, chambers, reservoirs, detection and processing regions. This makes it possible to exploit the key attributes of microfabricated chips and other miniature fluidic or analytical components in a conventional, cartridge-type, physical environment. Such a combination, while superficially less sophisticated than "lab-on-a-chip" technology, affords a superior blend of efficiency and convenience in design, manufacture, and use.

[0011] In a preferred embodiment, the invention provides a device for separating a desired analyte from a fluid sample and for concentrating the analyte into a volume of elution fluid smaller than the original sample volume. The desired analyte may comprise, e.g., organisms, cells, proteins, nucleic acid, carbohydrates, virus particles, bacterias, chemicals, or biochemicals. In a preferred use, the desired analyte comprises nucleic acid.

[0012] The device comprises a cartridge having formed therein an inlet port for introducing the sample into the cartridge and a sample flow path extending from the inlet port through the body of the cartridge. The sample flow path includes an analyte capture region having at least one flow-through component for capturing the desired analyte from the sample.

[0013] The flow-through component is preferably a microfabricated chip having a chamber with internal microstructures formed therein. The microstructures have sufficiently high surface area and binding affinity with the desired analyte to capture the analyte as the sample flows through the chip.